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ORIGINAL ARTICLE

Maximizing retention in long-term clinical trials of a weight loss agent: use of a dietitian support team

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Summary

Objective

High-attrition rates have been observed in long-term clinical trials of weight loss agents. We evaluated the impact of an innovative retention programme on 1-year retention.

Methods

Three Phase 3 global multicentre clinical trials evaluated the efficacy and safety of a CB1 receptor antagonist in subjects with BMI $\geq$ or = 27 kg/m^2. The impact of a multifaceted retention programme including a dietitian screening interview, a comprehensive culturally adapted lifestyle modification programme, and a dietitian support system to maximize lifestyle adherence, was evaluated in 4,410 subjects from four subpopulations (non-US English-speaking, non-English-speaking, US-without dietitian screening and US-with dietitian screening) comprising 208 centres from 15 countries.

Results

The median proportion retained over the first year among subjects in three protocols was 82%. Non-English-speaking countries showed higher retention rates (89%) compared with the USA (73%) and non-US English-speaking (81%) countries. Within the USA, behavioural screening was associated with 29% reduction in dropout rate; for every five monthly teleconferences attended above 11, there was a 32% decrease in dropout rate.

Conclusions

This novel retention programme greatly improved upon reported retention rates of studies conducted with other weight loss agents in long-term clinical trials. Its effectiveness should be confirmed in future trials.

Keywords: clinical trial, obesity, retention, type 2 diabetes, weight management.

Introduction

The inability of most patients to sustain lifestyle changes long-term has made pharmacotherapy an attractive option in obesity management. However, the approval process for new weight loss agents involves lengthy and costly clinical development programmes to meet efficacy, safety and tolerability regulatory requirements.

Randomized controlled trials of weight loss agents have been severely criticized because of high-attrition rates. On average, one-third to one-half of participants drops out of these large trials by 1 year (1–5). Such high-attrition rates result in missing data that limit the interpretation and generalizability of findings (6). Limiting attrition is, therefore, an important objective in obtaining reliable and valid study results.

All clinical trials of weight loss agents apply some form of lifestyle modification as a regulatory requirement (7,8). This requirement can potentially bring important benefits. A lifestyle modification programme when used in combination with a weight loss drug can result in greater total weight loss and contribute to a more positive health impact. For example, when sibutramine (15 mg/d) was added to a lifestyle modification programme, the weight

loss achieved at 12 months was nearly double that of each treatment alone (9). Additionally, the integration of lifestyle modification programmes into clinical trials of weight loss agents is highly valued by study participants and so can play a key role as a strategy to increase adherence and retention (10,11).

Interestingly, dropout rates have been significantly higher in pharmaceutical trials of weight loss agents compared with long-term clinical trials implementing lifestyle intervention programmes which have also targeted weight loss efficacy (12–14). For instance, in the Diabetes Prevention Program (DPP), which randomly assigned overweight subjects to receive a lifestyle intervention, the medication metformin or placebo, the dropout rate was only 6% after an average of 2.8 years of the lifestyle intervention (14). The majority of discontinuations in industry-sponsored weight loss studies are due to treatment dissatisfaction and practical difficulties (9,15,16).

The planning of this pharmaceutical trial which was seeking a weight loss indication for a cannabinoid receptor antagonist (CB1 blocker) included a decision to prioritize efforts to maximize retention outcomes. In an attempt to reduce the dropout rate, this global Phase 3 programme included a comprehensive and standardized lifestyle modification programme adapted from DPP (17) that included ongoing contacts with a dietitian, alternating face-to-face with telephone contacts, and culturally sensitive lifestyle intervention materials as part of the retention strategy. While previous studies have used mental health professionals, nurses or bachelor's or master's level researchers to screen participants, our approach was to model a retention programme based on strategies used in DPP (18); including a dietitian in the screening process and a dietitian support system that involved sharing approaches to increase lifestyle adherence and retention of both dietitian interventionists and study participants during long-duration trials. This paper describes the components of an innovative dietitian support programme designed to maximize retention in long-term clinical trials of weight loss agents, its impact on dropout rates and its potential use as a model in future pharmaceutical industry-sponsored studies for the development of weight loss agents.

Methods

Study design

Three Phase 3, double-blind, placebo-controlled and multicentre clinical trials, were conducted to evaluate the long-term efficacy and safety of CP-945,598 (CB1 receptor agonist) in the treatment of persons with overweight or obesity with or without type 2 diabetes (T2D) at doses of 10- and 20-mg once daily orally (19). Two of the trials, one run entirely in North America (NA2) and the other multinational (MN2), were weight loss studies designed to be 2 years in duration with 10 mg, 20 mg and placebo, randomized 1:1:1. The third study (DM1) was a 1-year weight loss study of T2D (allocation 1:1.5:1). Differences among the three studies are summarized in Table 1. The primary efficacy endpoint in all trials was change in body weight from baseline to week 52.

Based on changes in regulatory perspectives with regard to the risk/benefit profile of CB1 receptor-related drugs and the likely difficulties of obtaining regulatory approval for them, a decision was made to discontinue the three trials and the entire CP-945,598 development programme in November 2008. By that time, the majority of patients in the three trials had completed at least 1 year of dosing with CP-945,598.

Participants

Participants included men and women, aged 18–70 years, with BMI $\geq$30 kg/m^2 for participants without comorbidities and $\geq$27 kg/m^2 for those with hypertension or dyslipidemia. Participants in the 1-year study also had T2D. Details of baseline and demographic profiles, inclusion and exclusion criteria and study procedures have been described in detail (19).

The retention programme

The study included a multifaceted retention programme consisting of the following:

Table 1 Distinguishing features of three Pfizer Phase 3 weight loss studies

Study	T2DM diagnosis	Duration (years)	Number countries	Number centres	Randomized subjects	Subjects analyzed*
MN2	No	2	11	62	1,253	1,141
DM1	Yes	1	12	88	975	837
NA2	No	2	2	77	2,536	2,432

*Subjects who had weight loss data.
DM1, third study; MN2, multinational; NA2, North America; T2DM, type 2 diabetes.

- The participation of a dietitian, when possible, in the screening of potential volunteers
- A comprehensive lifestyle intervention supported by culturally adapted printed materials and delivered through periodic face-to-face or telephone interactions with a dietitian
- A novel dietitian support system to ensure lifestyle adherence and treatment fidelity for both dietitians and study participants

Behavioural screening

Potential study participants were asked to complete at least five of 7 days of food and physical activity records after the first screening visit, to be eligible for randomization. The dietitian's behavioural screening interview involved two components (i) reviewing the food and activity logs for completion and accuracy and (ii) conducting behavioural interviews to assess motivations for participating in the study, weight loss history, past experiences with weight loss, ability to commit to study visit schedule, anticipated significant life events, weight loss expectations and ability to commit to the goals of each treatment assignment. The dietitians then shared their insights with study teams regarding suitability of volunteers for study inclusion in terms of readiness to enter a weight loss programme and ability to commit to the requirements of a research trial. The screening interview visit also served as an opportunity for the dietitians to start building a therapeutic relationship with each participant prior to the start of the lifestyle intervention; this would form the basis of enhancing retention throughout the intervention.

Lifestyle intervention

All three trials included a comprehensive diet and exercise programme involving behavioural modification with support of a dietitian (a healthcare professional with experience in lifestyle counselling for obesity treatment was used instead by a few non-US centres that did not have access to a dietitian).

The behavioural strategies and support materials were adapted from DPP's lifestyle intervention and addressed a variety of nutrition, activity and behavioural topics (17). All subjects were instructed to adopt a 500–750 kcal d^{-1} deficit diet. Calorie goals were calculated based on each patient's baseline body weight and caloric requirements for weight maintenance using the Institute of Medicine estimated energy requirement formula (20). Fat gram goals were based on 25% of calories from fat. All subjects were given a pedometer and recommendations to increase their number of steps per day by approximately 500 steps each week and build to a goal of 60–90 min or 10,000 steps per day. Behavioural treatment strategies included goal-setting, self-monitoring (including weekly weighing and completion of daily food intake and physical activity logs), stimulus control, enlisting support of family and friends, use of problem-solving skills to overcome barriers, cognitive restructuring, stress management and coping with lapses. All subjects received the same printed support materials, which included a diet and exercise guide (DEG). The DEG was adapted for worldwide use, translated into different languages and revised to ensure compatibility with local lifestyle and culture.

The lifestyle intervention was delivered and reinforced alternating face-to-face with telephone contact with a dietitian, weekly or biweekly during the first 6 months and monthly thereafter (19). The behavioural sessions were generally delivered by the same provider throughout the study. Face-to-face sessions took about 30 min and telephone interactions about 15 min. Dietitians reviewed diet and exercise logs with participants and DEG lessons, trying to keep subjects motivated, identifying early signs of dropout and providing solutions to potential adherence barriers.

Dietitian support system

Dietitians were supported by a team of healthcare professionals with experience in obesity trials, lifestyle intervention and retention strategies. This Dietitian Support team, organized by the last author and led by the first author, provided training on delivering the lifestyle intervention and on strategies to maximize adherence and retention.

The support programme included the following key components (i) a global in person dietitian training programme; (ii) monthly teleconferences to coach dietitians on strategies to enhance lifestyle intervention adherence and maximize retention; (iii) a query system to address frequently asked questions related to intervention delivery and case management concerns; (iv) monthly newsletter articles to address important retention and intervention topics and (v) refresher webinars.

The global in person training programme provided training on how to enhance the delivery of the lifestyle intervention, outlining the primary goals of each session and emphasizing key messages, discussion questions and skills to focus on with study participants for each nutrition, activity and behavioural topic. The in person retention training programme focused on both proactive strategies to maintain participant engagement and reactive strategies to minimize dropout of at risk participants. Based on experience with the DPP, a key proactive-retention strategy was to train study dietitians to conduct a behavioural screening interview to assess participant readiness to commit to the weight loss intervention prior

to proceeding with a decision to enroll the subject. Other retention strategies included training on skills to maximize adherence to the intervention, minimize the effects of non-adherence on retention, identify signs and predictors of retention problems and respond with strategies to maintain participant engagement after randomization.

As part of the retention programme, dietitians were trained to detect early warning signs of dropout. Dietitians learned to be mindful of comments made during the screening interview and to pay attention to patterns of attendance, ease of access via phone or email, weight change patterns; attitudes about scheduling appointments, completing food records and progress with weight and activity. Changes in work or travel schedule or life stressors were also assessed. They were coached to focus on strategies to build self-efficacy, help participants reframe negative thinking through cognitive restructuring and when needed to negotiate for minimum acceptable participation levels with participants who expressed a desire to withdraw from the study. On the monthly calls, the dietitians discussed challenging cases, received tailored coaching and shared successful strategies with other dietitians.

The monthly conference calls were organized to include 8 to 10 dietitians per call. The initial monthly calls focused on skills for conducting and interpreting the behavioural screening interview. Later conference calls focused on updates on recruitment and the behavioural screening process, intervention progress and retention metrics at each site, sharing of strategies and ideas to enhance intervention delivery and adherence, and a case discussion and problem-solving approach to address retention concerns.

Dietitian queries were handled during monthly teleconferences or via e-mail. A frequently asked question document was created to document responses and was continuously updated over the course of the trials and circulated to the dietitians to assure consistency in approach among dietitians and programme coordinators study-wide. If a query could not wait to be discussed at the monthly teleconference, dietitians were encouraged to send the query via e-mail to the dietitian support team. The monthly newsletter and refresher webinars provided study updates on retention metrics, lifestyle strategies and profiled successful retention initiatives at various clinical sites.

One dietitian representative from each site was asked to participate in the monthly teleconferences. A bilingual country dietitian leader was identified for non-English-speaking countries. The dietitian support team interacted directly with English-speaking dietitians and bilingual country dietitian leaders during monthly teleconferences. Country dietitian leaders held 1-h monthly teleconferences with their respective country dietitians to provide support and updates. Country dietitian leaders also helped review the DEG for cultural adaptation.

All study sites were strongly encouraged to have site dietitians participate in screening of potential subjects and in the monthly conference calls. The dietitians' involvement in participant screening at each site was queried, and attendance of site dietitians and bilingual country dietitians on monthly conference calls was polled and recorded over the full study period; however, country dietitian leaders did not keep attendance records of their calls with their country dietitians.

Outcomes

The primary endpoint in this retention study is the time each subject spent on study from randomization to study medication (10 or 20 mg doses or placebo) to 1-year post-randomization, dropout or study cancellation, whichever occurred first. Subjects who completed 1 year or who were still participating at the time of cancellation were considered retained. Percent change from baseline body weight at subjects' latest assessment is an additional endpoint of interest.

Statistical analysis

For a variety of reasons, the retention and lifestyle intervention programmes could not be exactly replicated at

Table 2 Distinguishing characteristics of four post-hoc subpopulations

Subpopulation	Protocols	Screening dietitians	Site dietitians[†]	Number countries	Teleconference language
Non-English + dietitian	MN2, DM1	Yes	No	10	Multiple non-English
English* + dietitian	MN2, DM1 and NA2	Yes	Yes	4	English
USA – no dietitian	MN2, DM1 and NA2	No	Yes	1	English
USA + dietitian	MN2, DM1 and NA2	Yes	Yes	1	English

*Non-US English-speaking centres.
DM1, third study; MN2, multinational; NA2, North America.
[†]Site dietitian attendance records of participation in teleconferences.

all study centres. This situation resulted in four variants of the programme. Based on these variants, 208 study centres were grouped into four analysis subpopulations that differed from one another on the basis of the country, language spoken by dietitians and participation of centre dietitians in the screening visit and monthly dietitian teleconferences (Tables 2 and 3).

Two of the subpopulations composed of non-English-speaking and non-US English-speaking centres (e.g. United Kingdom centres) had dietitians involved in screening at all of their constituent centres. In contrast, US centres were divided into those who had a screening dietitian and those who did not. The association of the outcomes with several risk factors including the two-main components of the subject retention programme, (i) presence of centre's dietitian for a screening visit and (ii) attendance and participation in monthly teleconferences with centre-level or country-level dietitian leaders, was examined through statistical analysis of data from the four subpopulations.

The distribution of retention times was estimated for each subpopulation using Kaplan–Meier methods. Differential dropout rates associated with subgroup membership, centre-level and subject-level risk factors were estimated from stratified (on study protocol) Cox regression models (21). The rate differences of two comparison groups are expressed as ratios of their dropout rates (called hazards). A hazard ratio (HR), A/B >1.0, implies that subjects in group A drop out at a faster rate than subjects in B or, alternatively, that retention in A is reduced by 100*B/A% relative to B. Because individual centres in the non-English subpopulation did not have dietitians who participated in the dietitian teleconferences, the effects of teleconference attendance on dropout risk could not be assessed in any model that included the non-English subpopulation. Thus, two separate Cox models were

Table 3 Composition of subpopulations, by protocol and participating country

Subpopulation	Protocol	Country	Dietitian at screen	Number centres $n = 208$	Total subjects $n = 4{,}410$	Percent of subjects retained at 1 year
Non-English + dietitian						
	MN2	Argentina	Yes	6	62	73
	MN2	Chile	Yes	3	89	82
	MN2	France	Yes	6	71	92
	MN2	Germany	Yes	6	224	82
	MN2	Mexico	Yes	1	15	93
	MN2	Spain	Yes	5	72	85
	MN2	S. Korea	Yes	4	91	89
	DM1	Argentina	Yes	3	29	72
	DM1	Brazil	Yes	6	73	82
	DM1	Czech Rep.	Yes	5	36	100
	DM1	Germany	Yes	5	30	83
	DM1	Mexico	Yes	5	74	69
	DM1	Slovakia	Yes	4	39	97
English* + dietitian						
	MN2	Australia	Yes	5	115	82
	MN2	Sweden	Yes	3	86	77
	MN2	UK	Yes	4	64	67
	DM1	Australia	Yes	5	76	91
	DM1	Canada	Yes	5	69	80
	DM1	Sweden	Yes	2	7	86
	DM1	UK	Yes	5	22	82
	NA2	Canada	Yes	6	190	65
USA – no dietitian						
	MN2	USA	No	4	79	65
	DM1	USA	No	7	72	64
	NA2	USA	No	14	463	52
USA + Dietitian						
	MN2	USA	Yes	9	173	68
	DM1	USA	Yes	26	310	73
	NA2	USA	Yes	54	1779	67

*Non-US English-speaking centres.
DM1, third study; MN2, multinational; NA2, North America.

employed to estimate risk factor effects. One model was fit to data from all 4,410 subjects from the four subpopulations, while the other was fit to 2,876 subjects from the two US subpopulations. Both models estimated dropout risks associated with gender, race, age and treatment group. The differential risks associated with subpopulation membership were estimated in the full data set while dropout risks associated with presence of a screening dietitian were estimated using the two US subpopulations.

Percent change from baseline body weight at the subjects' latest evaluation within their first year on study was analyzed by fitting an analysis of covariance model to the log-scale changes from baseline with the natural log of the baseline weight as a covariate and the same centre-level and subject-level-risk factors as described for the Cox models. All models provided estimates of treatment and covariate effects, adjusted for all other factors in the models.

Results

Of 4,764 randomized subjects, only 4,689 had useable weight loss data. Of these, 277 subjects lacked data on dietitian participation at screening and two more had missing gender data, leaving 4410 subjects from 208 centres for analysis (Table 3). Among the country by protocol groups in Table 3, the proportions of subjects retained ranged from 52% (US subpopulation with no dietitian screening in Study NA2) to 100% (Czech Republic, with dietitian screening in Study DM1) with a median of 82%. Generally, the US centres had more subjects, fewer days on study and higher dropout rates than centres in the other two subpopulations. By contrast, the non-English centres had the fewest subjects, the best teleconference attendance, the most time on study and the smallest dropout rate of all the subpopulations (Table 4). However, the great majority of the non-English centres were represented in teleconferences by a single country-level dietitian, whereas each of the centres in the other subpopulations was represented by its own dietitian. Consequently, teleconference attendance is not directly comparable in non-English vs. other subpopulations.

The retention relationships among the four subpopulations that are evident in Tables 3 and 4 are more clearly displayed in Kaplan–Meier plots (Figure 1). Retention declines slowest and least for the non-English subpopulation and fastest and most for the US subpopulation without a screening dietitian. The inclusion of dietitian screening interview in the US population reduced the dropout rate by 10% 1-year post-randomization.

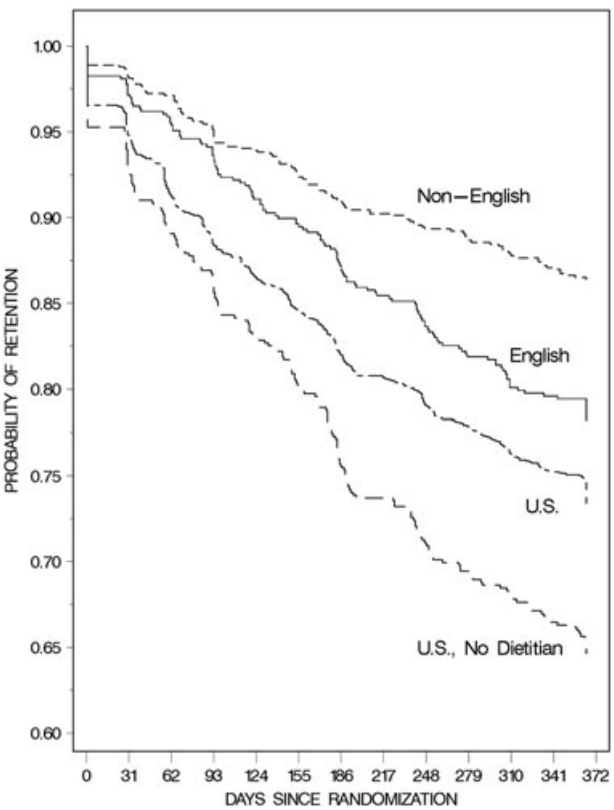

Figure 1 Kaplan–Meier cumulative retention probability plots vs. time on study for the four study subpopulations. Probabilities of staying on study for 1 year were 0.65 for the subjects from US centres without a screening dietitian, 0.75 for US centres with a screening dietitian, 0.79 for non-US English-speaking subjects at centres with a screening dietitian and 0.87 for non-English-speaking subjects at centres with a screening dietitian.

Table 4 Median measures of time on study and retention programme participation, by analysis subpopulation

Centre-level covariate	Non-English*	Non-US English†	USA no dietitian†	USA + dietitian†
No. subjects/CTR	12	17	30	31
Total no.TCs attended	15	7	8	13
No. days in study	345	327	301	308
% Dropout	11	19	30	25

*Attendance by country-level dietitians.
†Attendance by centre-level dietitians.

The HR estimates for differential retention due to effects of sex, race, treatment and a 5-year increase in age obtained from the stratified (on protocol) Cox Model for all four subpopulations are summarized in Table 5. The HR estimates for the subpopulation comparisons are consistent with the Kaplan–Meier plots. Perhaps most noteworthy, the dropout rate in the only subpopulation that did not have a dietitian present at screening was significantly greater than the rates relative to any of the other subpopulations (HRs = 1.41–3.54). Conversely, rate of dropout was significantly greater in all subpopulations relative to the non-English subpopulation. Blacks, Whites and 'other' racial groups all experienced significantly greater dropout rate than Asians.

The Cox model results for the analysis restricted to the US centres (Table 6) revealed that the inclusion of a

Table 5 Summary of hazard ratio estimates from the stratified (on protocol) Cox model fit to the full data set (208 centres and 4,410 subjects)

Main effect	Comparison group	Reference group	Hazard ratio (95% conf. int.)
Subpopulation			
	USA no dietitian	USA + dietitian	1.41 (1.21, 1.66)*
	USA no dietitian	English† + dietitian	1.53 (1.21, 1.93)*
	USA no dietitian	Non-English + dietitian	3.54 (1.94, 3.33)*
	USA + dietitian	English† + dietitian	1.08 (0.88, 1.34)
	USA + dietitian	Non-English + dietitian	1.79 (1.39, 2.31)*
	English† + dietitian	Non-English + dietitian	1.66 (1.27, 2.17)*
Race			
	Other	Black	0.98 (0.75, 1.30)
	Other	White	1.27 (1.03, 1.61)*
	Other	Asian	2.12 (1.18, 3.78)*
	Black	White	1.29 (1.08, 1.55)*
	Black	Asian	2.15 (1.20, 3.84)*
	White	Asian	1.66 (0.95, 2.89)
Age increase			
	5 years older	5 years younger	0.83 (0.81, 0.86)*
	10 years older	10 years younger	0.69 (0.66, 0.74)*
	20 years older	20 years younger	0.48 (0.43, 0.54)*

*Statistically significant ($\alpha = 0.05$).
†Non-US English-speaking centres.

Table 6 Summary of hazard ratio estimates from the stratified (on protocol) Cox model fit to the pooled US subpopulations (114 centres and 2,876 subjects)

Main effect	Comparison group	Reference group	Hazard ratio (95% conf. int.)
Dietitian at screening	Absent	Present	1.33 (1.12, 1.57)*
Race			
	Other	Black	0.98 (0.71, 1.35)
	Other	White	1.28 (0.96, 1.71)
	Other	Asian	1.48 (0.70, 3.15)
	Black	White	1.31 (1.08, 1.58)*
	Black	Asian	1.51 (0.74, 3.10)
	White	Asian	1.16 (0.57, 2.33)
Age increase			
	5 years older	5 years younger	0.83 (0.81, 0.86)*
	10 years older	10 years younger	0.69 (0.65, 0.74)*
	20 years older	20 years younger	0.48 (0.42, 0.55)*
Total attendance increase (13–24 TCs attended)			
	13 TCs	12 TCs	0.93 (0.89, 0.96)*
	14 TCs	12 TCs	0.86 (0.79, 0.93)*
	17 TCs	12 TCs	0.68 (0.56, 0.83)*

*Statistically significant ($\alpha = 0.05$).

dietitian at screening, age and total teleconferences attended significantly affected dropout rate. The HR of dropout for subjects from sites without a dietitian at screening was 1.33 times greater than for US subjects at centres that had a screening dietitian. The HR estimates due to age in the USA only centres were nearly identical to those in the four-subpopulation analysis.

Figure 2 illustrates the effects on 1-year retention due to age and teleconference attendance over their range in the study subpopulations. While the effect of age is clearly linear, the effect of teleconference attendance by the site dietitians did not exert a consistent effect on 1-year retention until a dietitian had attended 11 teleconferences, above which the probability increased linearly with increasing attendance.

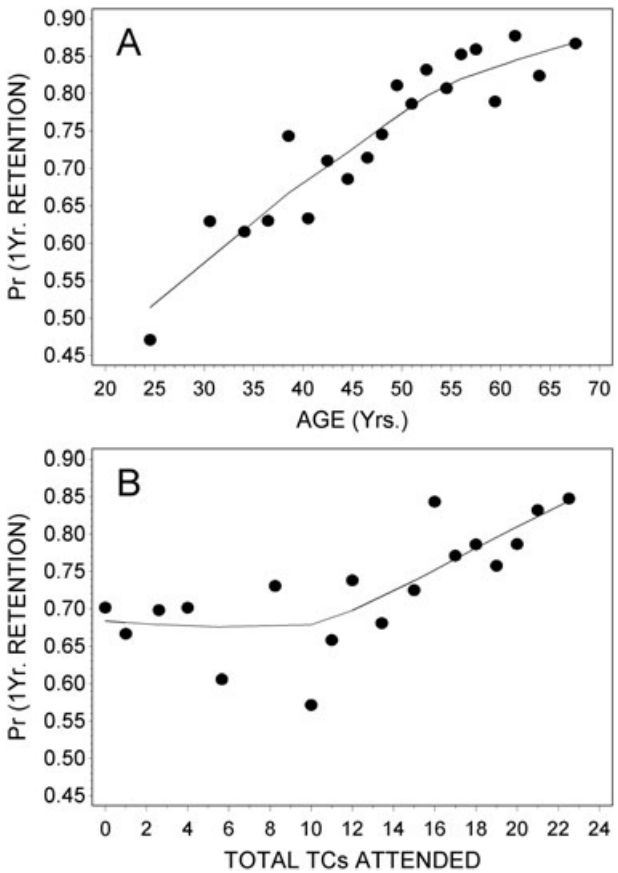

Figure 2 Retention probability vs. vigentiles of (a) age in the full data set ($n = 4{,}410$) and (b) teleconference attendance in the three English-speaking subpopulations ($n = 3{,}505$). Each point = 1 vigentile = 1/20th of the population. Vigentiles were formed by first ordering the populations by age and then by teleconference attendance and then dividing them into 20 groups of equal size (approximately 220 per group in the full data set and 175 per group in the pooled English-speaking subpopulations). Loess nonparametric regression lines are overlaid on each set of Vigentiles.

There were no significant differences in percent weight loss among the four subpopulations (means ranged from −4.1% to −4.4%) nor were there significant differences in weight loss due to presence of a dietitian at screening or numbers of teleconferences attended among subjects in the US subpopulations. Consistent with Aronne *et al.* (15), the therapeutic treatments significantly affected weight loss (−2.8%, −4.4% and −5.7% respectively in placebo, 10 and 20 mg treatment groups).

Discussion

We implemented a comprehensive retention programme within three Phase 3, double-blind, placebo-controlled, multicentre clinical trials of persons with overweight and obesity with and without diabetes and achieved 73% retention in the USA, 81% retention in non-US English-speaking countries and 89% retention in non-English-speaking countries at 1 year. This retention programme was implemented proactively and was successful at improving upon the reported 53% 1-year retention rate in the Rio-North American study, which studied a similar weight loss drug in patients with similar BMI but without diabetes in the USA and Canada, also over a 1-year time period (1,19), and even improved upon the retention rate of Phase 3 trials conducted with more recently approved weight loss agents (2–5).

The higher retention rates achieved in the non-US and non-English-speaking countries vs. the USA may be due to a more proactive engagement of these sites in the retention programme as shown by inclusion of the dietitian in screening from the outset of the trial and overall somewhat better teleconference participation. A higher patient retentive environment in terms of better adherence to trial protocols, stronger local physician–patient relationships and a largely trial naive patient population that may gain access to a higher standard of care through trial participation (22), may have also contributed.

The USA was the only country in which there were sites that lacked a dietitian at the screening visit. Those sites had a Kaplan–Meier-estimated 10% higher year-1 dropout probability and dropped out 1.41 times faster than subjects in US sites that utilized a screening dietitian during year-1. Greater attendance at monthly dietitian support conference calls in the USA was associated with greater retention results as well, such that for every five calls attended, there was a 32% decrease in dropout rate. The effect of attendance was not strictly linear because it appears that the benefits accrued only to study centres whose dietitian attended more than 11 teleconferences. This may reflect the time needed for dietitians to integrate new knowledge and skills, and refine expertise related to

maximizing retention and outcomes. The association of retention with increased teleconference attendance may indicate that attendance reflects differential commitment of centres to the protocol procedures (including teleconference attendance). There have been many studies examining pretreatment and process predictors of dropout in weight loss interventions (11,13,15,16). However, few studies have utilized this evidence base to develop and implement screening tools and retention approaches to assess and manage known predictors of dropout (11). Innovative retention programmes such as this one that identify those individuals most at risk of dropout and provide those who enroll with the support that they need to benefit from the treatment will contribute to both the effectiveness and cost-effectiveness of weight loss interventions. When pressures and incentives are primarily focused on meeting enrollment targets, then clinical centres do not proactively screen out volunteers who may represent a retention risk. Helping patients determine if study goals and expectations are a good fit in terms of interest, commitment and timing minimizes the experience of treatment failure for both the clinical programme and the patient, maximizes retention, and facilitates a discussion of more suitable treatment alternatives or timing of enrollment.

Strengths of this study include the large-sample size of persons with overweight and obesity with and without diabetes, use of a retention programme including a comprehensive lifestyle modification programme and targeting evidence-based predictors of dropout and prospective collection of retention programme metrics in terms of involvement of the dietitian in screening and attendance on monthly conference calls.

Our inability to randomize the retention programmes was a critical limitation of this study. Although the same programme was offered at all sites, not all sites participated in the programme to the same extent, and a few sites did not have access to a dietitian. As is common in nonrandomized studies, potential confounding of the risk factors with one another presented additional challenges to analysis and interpretation of time on study and dropout rates. In particular, there appeared to be potential for confounding of the retention programme participation with study protocol and the country in which the study centre was located. For example, while the lifestyle intervention materials and delivery were consistent across countries, more receptivity of non-US participants to lifestyle recommendations or even better delivery by non-US dietitians may have improved adherence to the trials.

Current initiatives (e.g. the Clinical Trials Transformation Initiative and the proposed National Center for Advancing Translational Sciences) and the recent Institute of Medicine report emphasize the critical importance of successful recruitment and retention strategies for improving efficiency and effectiveness of Phases 3 and 4 clinical trials, stating that action to ensure adequate enrollment and retention is urgently needed (23). Of particular concern is the failure of US trials to meet desired enrollment and retention targets and the trend towards increasing emphasis on recruitment abroad. One of the critical barriers to successful retention has been underestimating the financial realities associated with infrastructure needs and reimbursement costs for both recruitment and retention of study participants. Many trials have traditionally organized financial incentives for clinical sites based on patient enrollment but have not invested in infrastructure, incentives and expertise necessary for maximizing retention. Yet the cost implications of a need to enroll 25% more subjects to compensate for an increase in dropout rate from 20% to 40% to maintain an 80% power to detect a difference between two treatment groups are very real (23,24).

Conclusion

Use of an innovative retention programme that included a dietitian screening interview to identify patients at high risk of dropout and monthly support conference calls to discuss strategies to maximize adherence and retention appeared to be associated with better retention rates in global Phase 3 multicentre long-term clinical trials of a weight loss agent. This approach has potential for use in maximizing retention and cost-effectiveness of future pharmaceutical sponsored studies targeting the development of weight loss agents.

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Disclosures

L.M. Delahanty was paid as a consultant to Pfizer to design the retention strategy and lead its implementation. M. Riggs was paid as a consultant to do some of the statistical analyses prior to employment at Pfizer.

* A. Digenio, R. Chew, S. Klioze, R. England and M. Riggs were employees of Pfizer at the time the studies were conducted and/or during the preparation of this manuscript. R. Chew, S. Klioze, R. England, M. Riggs and A. Digenio currently own stock and stock options in Pfizer.

Author contributions

L. M. D., A. D. and M. R. wrote the initial draft of the manuscript. L. M. D., M. R. and R. D. C. contributed to the data analysis. L. M. D. and M. R. collected and organized the data. L. M. D., M. R., R. D. C., S. S. K., R. D. E. and A. D. reviewed/ edited the manuscript. The data for the studies herein described are held by Pfizer Inc. M. R. is the guarantor of this work, and as such, had full access to all the data from the studies and takes responsibility for the integrity of the data and the accuracy of their analyses presented in this paper.

Conflict of interest statement

No conflict of interest statement.

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